Evidence for a Non-Linear Dependence of Tumor Growth on Immune Response as Revealed by a Self-Metastatic Model for Tumor Growth

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Among mechanisms modulating tumor growth and potential escape of tumors from the dormant state is the immune response. In this regard, we note a key observation of Prehn [2006] and others that the efficiency of the immune system in eradicating the tumor could show a complicated dependence on the ratio of immune reactants to tumor cells. Prehn argued specifically that a low immune reaction could accelerate tumor growth, whereas a large numbers of immune reactants will inhibit progression. Leading propositions for the basis for this effect lie in inflammatory and/or cell-selective activity. Infiltrating macrophages and mast cells can regulate cell proliferation and cell death, for instance, and chronic inflammation can skew the dynamics in favor of tumor growth. Indirect effects such as angiogenic factors and MMP production have also been argued. Another proposition is that the immune system can keep the tumor in a somewhat dormant stage, but over time select for more aggressive variants with reduced immunogenicity. We have uncovered a novel, alternative mechanism that can explain the mixed tumor growth regulation by the immune response without invoking indirect secondary or evolutionary processes. We previously published on an agent-based *in silico* model of tumor progression that captures a phenomenon of self-metastasis, which can explain an anomalous trend to increased tumor growth following induction of apoptosis. We now show, including a diffusible, immune source into this construct, that the anomalous immune effects reported elsewhere can be explained by similar logic. We show specifically that it can be a natural consequence of basic cell kinetic interactions in a cytotoxic immune environment. Suggested is a non-linear dependence of final tumor risk on the level of immune response evoked by the growing tumor.

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